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Abstract

The incidence of type 2 diabetes (T2D) is increasing at an alarming rate, which is imposing substantial healthcare and economic burdens worldwide. T2D can be treated by a range of drugs, but there is a need to identify additional therapeutic options. Human islets express nearly three hundred G-protein-coupled receptors (GPCRs), which could be targeted for the treatment of T2D. However, to date, the GLP-1 receptor is the only islet GPCR for which agonists are in current clinical use. This review explores pharmaceutical development of drugs that activate individual or multiple beta-cell GPCRs and explains how our knowledge of GPCR expression by human islets may inform direction on novel GPCR targets.

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Highlights

- Type 2 diabetes (T2D) is a major healthcare concern.
- G-protein-coupled receptor (GPCR) ligands are used to treat a range of diseases.
- Human islets express nearly three hundred GPCRs.
- Only one islet GPCR is currently the target of a clinically used T2D therapy.
- Pharmaceutical companies are developing T2D therapies that activate islet GPCRs.

Islet G-protein coupled receptors: therapeutic potential for diabetes

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Abstract (100-120 words)

The incidence of type 2 diabetes (T2D) is increasing at an alarming rate, which is imposing substantial healthcare and economic burdens worldwide. T2D can be treated by a range of drugs, but there is a need to identify additional therapeutic options. Human islets express nearly three hundred G-protein-coupled receptors (GPCRs), which could be targeted for the treatment of T2D. However, to date, the GLP-1 receptor is the only islet GPCR for which agonists are in current clinical use. This review explores pharmaceutical development of drugs that activate individual or multiple β-cell GPCRs and explains how our knowledge of GPCR expression by human islets may inform direction on novel GPCR targets.

Introduction

G-protein-coupled receptors (GPCRs) have proven to be tractable targets for therapeutic intervention. For example, drugs targeting beta-2 adrenergic receptors on bronchial smooth muscle have been used to treat asthma for nearly 50 years [1], and antagonists of the AT1 angiotensin receptors were developed in the 1990s as effective anti-hypertensive drugs [2]. Over 800 human GPCR sequences have been identified [3] and it has been estimated that ligands targeting the GPCR superfamily account for 30-50% of all drugs that are in clinical use [4,5]. In fact, analysis of drugs that were approved by the US Food and Drug Administration over the three decades from 1982-2010 indicated that GPCRs are the largest class of targets for the development of new pharmaceutical products, with approximately 36% of all drugs reviewed acting at GPCRs [6]. In addition, 30% of the drugs with the highest global sales in 2010 targeted GPCRs [6].

Overview of therapies for Type 2 diabetes

Diabetes is a growing health concern and the incidence is continuing to increase at an alarming rate: the latest International Diabetes Federation data from Nov 2015 indicate that 415 million people worldwide had diabetes, and this is predicted to reach 642 million by 2040. Approximately 90% of people with diabetes have type 2 diabetes (T2D), which can be treated with a variety of drugs that directly stimulate insulin secretion from islet β-cells, improve sensitivity of peripheral tissues to circulating insulin, promote excretion of excess glucose in the urine or delay carbohydrate digestion (Table 1). The current front-line therapy for T2D, metformin, is an effective, inexpensive and well tolerated therapy, but there is a requirement for additional therapies when metformin is no longer capable of maintaining appropriate glucose homeostasis.

Of the many therapies in clinical use for T2D only GLP-1 analogues, which have been introduced in the last decade, are GPCR ligands. These drugs mimic the insulin stimulatory and glucagon inhibitory actions of the enteroendocrine cell-derived peptide GLP-1, which has a half-life of only 1-2 minutes. The GLP-1 analogues are long-acting through modifications of the peptide sequence. For example, exenatide (Byetta) lacks the N-terminal alanine at position 2 that is recognised by DPP4, a protease that cleaves and inactivates native GLP-1, and liraglutide (Victoza) contains a fatty acid residue to allow binding to albumin to extend its

circulating half life. DPP4 inhibitors, which prevent removal of the N-terminal dipeptide from GLP-1 and the other incretin hormone GIP, are also used clinically as insulin secretagogues. The increased circulating concentrations of incretin peptides with use of DPP4 inhibitors leads to enhanced signalling via their specific GPCRs on islet β-cells, both of which are coupled to elevations in intracellular cyclic AMP, thus promoting insulin exocytosis. The GLP-1 analogues act directly at GLP-1 receptors to have the same effect as endogenous GLP-1, but with prolonged duration of action. The currently prescribed GLP-1 analogues are reported to promote β-cell mass expansion in rodents [7], but similar beneficial effects have not been identified in humans [8].

Targeting islet GPCRs to develop novel therapies for Type 2 diabetes

While it is clear that there are numerous classes of drugs currently available to treat T2D (Table 1), only a minority of patients achieve full glycaemic control and there are potentially life-threatening side effects associated with some therapies [9]. In particular, there are concerns about the safety of therapies that are targeted at islet β-cells to promote increased insulin secretion to combat the insulin resistance that occurs in T2D. For example, sulphonylureas may induce dangerous hypoglycaemia and their long term use has been associated with increased incidence of coronary heart disease [10]. In addition, it has been proposed that prolonged sulphonylurea use is associated with progressive deterioration in beta-cell function [11], which could exacerbate the underlying pathology of T2D where there are reductions in β-cell mass [12]. The FDA issued a safety communication in 2013 that use of GLP-1 analogues has been linked to acute pancreatitis [13], but a recent meta-analysis of randomised clinical trials using a range of GLP-1 receptor agonists indicated that the incidence of pancreatitis was not increased with their use [14]. Nonetheless, the analysis did indicate an increased risk of cholelithiasis with GLP-1 analogues [14], and in 2016 an FDA warning was issued on severe and disabling joint pain associated with DPP4 inhibitor use [15]. These limitations in drug safety profiles and efficacy mean that the search for improved therapies is ongoing: since GPCRs have proven to be a successful target class for many indications [6] and GLP-1 mimetics now account for over 9% of the total diabetes market [16], pharmaceutical companies have been investigating the utility of targeting other islet GPCRs.

<u>Single GPCR targets</u>

Several β-cell-targeted T2D drugs have been under development in the past few years and there has been a focus on insulin secretagogue therapies that act at Gs- or Gq-coupled receptors. For example, FFAR1 (GPR40) is a Gq-coupled GPCR that is expressed by islet β-cells and also by the enteroendocrine L-cells that secrete GLP-1. This makes it a target of interest since selective agonists would be expected to stimulate insulin secretion through direct effects at β-cells or via indirect action to increase GLP-1 release, and GLP-1 also acts centrally to reduce food intake. Synthetic FFAR1 agonists have been effective in improving glucose tolerance in rodents [17,18], but development of FFAR1 agonists as T2D therapeutics has largely been unsuccessful and several potential candidates that entered clinical trials (Table 2) have been discontinued because of toxicity issues or unacceptable adverse effects. Nonetheless, phase I development is currently ongoing for some FFAR1 ligands (Table 2) and use of one of these (LY 2922470) in people with T2D has indicated that it exerts glucose lowering effects without hypoglycaemia [19]. GPR119, which is a Gs-coupled GPCR that is activated by the arachidonic metabolite N-arachidonoylethanolamine (AEA), has also been explored as a target for T2D therapy since this receptor is also expressed by β-cells and L-

cells. GPR119 agonists stimulate secretion of GLP-1 and insulin and they have glucose lowering effects in rodents [20]. However, it has recently become apparent through studies with β-cell-specific deletion of GPR119 that the presence of this receptor on β-cells is not required for GPR119 agonist-induced improvements in insulin secretion and glucose tolerance in mice [21]. Similar to FFAR1 agonists, apparently promising drugs that target GPR119 to improve glucose homeostasis in rodents have failed to progress beyond phase II clinical trials because of adverse effects or unfavourable study results (Table 2; [22]).

Multiple GPCR targets

An alternative strategy for T2D therapeutic development has been to antagonise the effects of the islet-derived peptide, glucagon, which acts at its GPCR on hepatocytes to stimulate glycogenolysis and gluconeogenesis [23]. Antagonism of these effects will therefore ameliorate the hyperglycaemia that is evident in T2D. Paradoxically, however, agonism of glucagon receptors could also be therapeutically viable since glucagon acts in a paracrine manner to promote insulin secretion and it also induces lipolysis and has anorexigenic effects, which are advantageous in T2D where the majority of individuals are overweight or obese. Given the effects of glucagon to increase hepatic glucose output glucagon receptor agonists on their own are not an appropriate therapeutic option. However, glucagon and GLP-1 chimeric peptides have been developed that act as co-agonists at glucagon and GLP-1 GPCRs, and these have been effective in reducing fat mass and improving glucose tolerance in obese mice [24]. There has been interest from pharmaceutical companies to harness these beneficial effects through the development of therapeutics that activate both glucagon and GLP-1 receptors. Some of these are currently being assessed in phase I or II clinical trials (Table 2), but patient recruitment has recently been suspended for at least one of these dual agonists (HM 12525A) pointing to potential problems with the use of this class of therapy. The reasons for suspension of the trial are not clear, but the effect of glucagon agonism at the liver to promote hyperglycaemia may be a contributory factor. Another strategy for dual agonist development has been to combine the insulin secretagogue effects of the incretins by generating single molecule drugs that activate both GLP-1 and GIP receptors, the so-called “twincretin” approach [25]. Both of these receptors are Gs-coupled to promote insulin secretion so activation of both islet incretin receptors should produce additive or synergistic glucose lowering effects. However, clinical trials with dual GLP-1 and GIP receptor agonists (Table 2) have not produced encouraging results and there currently appears to be no further activity in this area. The feasibility of polyagonists that activate GLP-1, GIP and glucagon receptors is being tested, with promising results in rodents, but clinical data are not yet available [26].

GPCR expression by human islets

Despite the appeal of exploiting GPCRs for development of novel T2D therapies, clinical trials have so far been based on very few islet GPCRs (Table 2), and the outcomes to date, as outlined above, have been disappointing. This lack of success may be because there is very limited scope in the receptors being targeted – so far potential therapies have been largely based on those activating FFAR1, GPR119 or incretin receptors, as indicated in Table 2. However, it is now apparent that human islets express mRNAs encoding 293 of the 384 functional non-odorant GPCRs encoded in the human genome [27], so there is plenty of opportunity for looking beyond the ‘usual suspects’. One interesting candidate that was identified by this GPCRome screening is the Gq-coupled receptor GPR75, which is activated by CCL5 (chemokine (C-C motif) ligand 5). CCL5 has direct effects on isolated mouse and human islets to potentiate glucose-induced insulin secretion and it also improves glucose

tolerance in mice [28]. CCL5 is not a suitable candidate for diabetes therapy as it also activates chemokine receptors implicated in β-cell destruction, but development of selective GPR75 agonists may be a promising route in improving therapeutic options for T2D. Another human islet GPCR that is currently receiving attention as a potential target for T2D therapy is GPR55, a putative cannabinoid receptor, which is coupled to direct stimulation of insulin secretion in vitro [29,30], and improvement in glucose tolerance in vivo in an incretin receptor-dependent manner [31].

Much of the research carried out on function of islet GPCRs in vitro has been performed using rodent islets and, by necessity, all basic science in vivo studies are performed using rodent models. There is usually a close correlation between the rodent and human experimental data, but there are occasionally divergences and it is obviously essential that data generated in mice and rats are translatable to the human situation. A recent study has indicated that while there is close correlation between the most abundantly expressed human and mouse islet GPCRs there are 63 mouse islet GPCRs that are not expressed by human islets [32]. This highlights the importance of the human islet GPCRome in defining clinically relevant therapeutic targets.

Conclusions

This short review has focused on islet GPCRs as possible targets for treating T2D, but, of course, this is an over-simplification: while islets express nearly three hundred GPCRs these receptors are not confined to islets, but are expressed by many other tissues too. In some respects this can be useful. For example, the GLP-1 analogues that are currently used to treat T2D act directly at islet β-cells to stimulate insulin secretion, but they have additional glucose regulatory effects through hypothalamic signalling to reduce food intake and they also act at the gut to delay gastric emptying. In addition, the FFAR1 and GPR119 agonists that have been under development for T2D are attractive because they are expressed by β-cells and L-cells, which should lead to improved glucose tolerance through stimulation of insulin release both directly and indirectly via enhanced GLP-1 secretion. However, as investigations progress on novel islet GPCR candidates it will be important to consider potential contra-indications that could arise through off-target effects at other tissues.

It is also important that the capacity of drugs to promote the survival and proliferation of insulin producing β-cells is fully considered when deciding which potential therapeutics to take forward to clinical trial, as without maintained β-cell mass people with T2D will eventually require exogenous insulin to maintain their blood glucose levels in the appropriate range. This can be problematic as while it is easy to quantify insulin secretagogue effects of drugs in humans there are currently no standardised methods for non-invasive quantification of human β-cell mass in vivo. Surrogate measurements of β-cell mass in humans suggest that the promising effects of GLP-1 analogues to promote β-cell proliferation and protect against apoptosis in rodents do not occur in humans, so there is plenty of scope to identify GPCR ligands that not only potentiate glucose-stimulated insulin release but also promote the survival and proliferation of insulin-producing β-cells.

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**This article quantified the expression of GPCR mRNAs in isolated mouse and human islets and commented on the necessity of considering whether mouse islets are a suitable surrogate for human islets in functional analyses of GPCRs of interest.

Table 1: Drug families currently used for treating Type 2 diabetes and their modes of action.

The table includes the classes of non-insulin therapies available for treatment of Type 2 diabetes, together with brief information on their modes of action. Examples of clinically prescribed drugs are provided for each family.

Main effect	Drug family	Mode of action	First introduced
Increase insulin secretion	Sulphonylureas Glibenclamide (Daonil) Glimepiride (Amaryl)	Close β-cell K_{ATP} channels leading to decreased K^+ efflux, membrane depolarisation, Ca^{2+} influx and enhanced insulin secretion.	1950s
	Glinides Nateglinide (Starlix) Repaglinide (Prandin)	Same mode of action as sulphonylureas, but glinides are shorter acting.	1990s
	GLP-1 analogues Exenatide (Byetta) Liraglutide (Victoza)	Have the same actions as the short-lived incretin peptide GLP-1 to activate β-cell GLP-1 receptors, increase cyclic AMP levels and activate protein kinase A to increase insulin secretion.	2000s
	DPP4 inhibitors Vildagliptin (Galvus) Sitagliptin (Januvia)	Inhibit the proteolytic action of DPP4, thus increasing levels of endogenous GLP-1 (and GIP), which can stimulate insulin secretion through elevations in cAMP (as for GLP-1 analogues).	2000s
Increase insulin sensitivity	Biguanides Metformin (Glucophage)	Activate AMP kinase in the liver to reduce gluconeogenesis.	1950s
	Thiazolidinediones Pioglitazone (Actos)	Bind to nuclear PPARγ receptors to stimulate transcription of anabolic genes, resulting in enhanced glucose and fatty acid uptake into adipocytes.	1990s
Increase glucose excretion	SGLT2 inhibitors Canagliflozin (Invokana) Dapagliflozin (Forxiga)	Inhibit SGLT2 transporters in the kidney proximal tubules to block glucose re-uptake into the blood so excess glucose is excreted in the urine.	2010s
Delay carbohydrate digestion	α-glucosidase inhibitors Acarbose (Glucobay) Miglitol (Glyset)	Competitively inhibit α-glucosidase enzymes on intestinal enterocytes toreduce cleavage of oligosaccharides. This delays completion of carbohydrate digestion so reduces elevations in glucose after a meal.	1990s

Table 2: Islet GPCR agonists that have been used in clinical trials for Type 2 diabetes. The table includes a non-exhaustive list of agonists developed by a range of pharmaceutical companies that target GPCRs expressed by human islets. It also includes the highest development phase of clinical testing for each drug.

Target	Drug	Highest Development Phase	Pharmaceutical Company
SINGLE AGONISTS			
FFAR1 (GPR40)	AMG-837	Phase I	Amgen
	ASP-4178	Phase I	Astellas
	LY 2881835	Phase I	Eli Lilly
	P 11187	Phase I	Piramal Enterprises
	Fugeliefan	Phase I	Jiangsu Hengrui
	LY 2922470	Phase I	Eli Lilly
	JTT 851	Phase II	Japan Tobacco
	TAK-875	Phase III	Takeda
GPR119			
	BMS 903452	Phase I	Bristol-Myers Squibb
	MBX 2982	Phase II	CymaBay Therapeutics
	PSN821	Phase II	Prosidion
	LEZ 763	Phase II	Novartis
	DS 8500	Phase II	Daiichi Sankyo Company
CO-AGONISTS			
GLP-1 receptor and glucagon receptor	ZP 2929	Phase I	Zealand Pharma
	MK 8521	Phase II	Merck & Co
	HM 12525A	Phase I	Janssen Pharmaceuticals
	LY 2944876	Phase II	Eli Lilly
	MEDI-0382	Phase II	MedImmune
GLP-1 receptor and GIP receptor	SAR 438335	Phase I	Sanofi
	RG 7697	Phase II	Roche
	NN9709	Phase II	Novo Nordisk

Islet G-protein coupled receptors: therapeutic potential for diabetes

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Conflicts of interest: none